

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES / ___ / NO / ___ / Explain: _____

Investigation #2

IND # _____ YES / ___ / NO / ___ / Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES / ___ / Explain _____ NO / ___ / Explain _____

Investigation #2

YES / ___ / Explain _____ NO / ___ / Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / ___ /

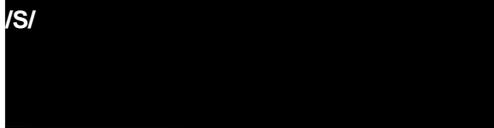
NO / ___ /

If yes, explain: _____

/s/

 7-7-99
Alice Kacuba
Regulatory Health Project Manager/Date

/s/

 7-7-99
Lilia Talarico, M.D.
Director/Date

cc: Original NDA 20-951
HFD-180/Division File
HFD-93/Mary Ann Holovac APPEARS THIS WAY ON ORIGINAL
HFD-180/A.Kacuba
HFD-560/A.Rothschild

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SB
SmithKline Beecham
Consumer Healthcare

Janice McSherry
Legal Counsel

DEBARMENT CERTIFICATION

Pursuant to section 306(a) and (b) of the Federal Food, Drug, and Cosmetics Act [21 USC 335(a) and (b)], and to the best of my information, knowledge and belief, no one involved in the development of this New Drug Application who has been or is currently employed by SmithKline Beecham Consumer Healthcare, has been debarred. Additionally, there are no debarment procedures pending for any current or past employee of SmithKline Beecham Consumer Healthcare. This was determined by comparing the current debarment list, dated April 4, 1997, to the listing of past and present SmithKline Beecham Consumer Healthcare employees.

Further, we certify SmithKline Beecham Consumer Healthcare will not use the services in any capacity of anyone debarred by the United States Food and Drug Administration.

We are not aware of any relevant convictions of SmithKline Beecham Consumer Healthcare personnel for which an individual can be debarred as described in section 306(a) and (b).

Janice McSherry
Janice McSherry, Senior Counsel

12/23/97
Date

SECTION 13

PATENT INFORMATION

CIMETIDINE SUSPENSION (1%)

1. Active Ingredient: Cimetine Polymorph-B
2. Strength: 200 mg/20 mL
3. Trade Name: Tagamet HB 200[®]
4. Dosage Form, Route of Administration: Suspension
5. Applicant and Firm Name: SmithKline Beecham Consumer Healthcare
6. NDA Number Assigned: 20-951
7. Approval Date: Submitted for review on December 29, 1997
8. Exclusivity - Date first ANDA could be approved and length of exclusivity period: To be determined pending FDA review and approval
9. Applicable patent numbers and expiration date of each:
(See attached patents; List below)

<u>Patent Number</u>	<u>Type of Patent</u>	<u>Patent Owner</u>	<u>Expiration Date</u>
4,786,735	Process	SmithKline Beckman Corp.	2008
4,996,222	Formulation	SmithKline & French Lab.	2011

United States Patent [19]

Carlín et al.

[11] **Patent Number:** 4,996,222

[45] **Date of Patent:** Feb. 26, 1991

[54] **PHARMACEUTICAL FORMULATIONS**

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[21] **Appl. No.:** 490,851

[22] **Filed:** Mar. 9, 1990

Related U.S. Application Data

[63] Continuation of Ser. No. 79,198, Jul. 29, 1987, abandoned.

[51] **Int. Cl.³** A61K 31/415

[52] **U.S. Cl.** 514/400

[58] **Field of Search** 514/400

[56] **References Cited**

FOREIGN PATENT DOCUMENTS

138540 4/1985 European Pat. Off. .
104868 8/1981 Japan .

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[57] **ABSTRACT**

The invention provides pharmaceutical suspension compositions of cimetidine wherein substantially all of the cimetidine is in the polymorph B crystalline form.

16 Claims, No Drawings

PHARMACEUTICAL FORMULATIONS

This is a continuation of application Ser. No. 07/079,198 filed July 29, 1987, now abandoned.

This invention relates to new pharmaceutical compositions and methods for their preparation, and in particular it relates to suspensions comprising cimetidine.

Cimetidine is a histamine H₂-antagonist which has been used for a number of years in the treatment of duodenal and benign gastric ulceration, recurrent and stomal ulceration, oesophageal reflux disease and other conditions where reduction of gastric acid by cimetidine has been shown to be beneficial, for example persistent dyspeptic symptoms with or without ulceration. It is widely recognised that there are considerable technical difficulties in producing stable and acceptable pharmaceutical compositions of cimetidine, particularly liquid solution and suspension compositions. Firstly, there is the difficulty of polymorphism which gives rise to problems of polymorphic transitions and crystal growth. It is generally recognised that cimetidine can exist in at least 5 different polymorphic forms and that these polymorphic forms differ in crystal habit and crystallisation properties, thermodynamic stability, and solubility and rate of dissolution in water. It is generally recognised that the polymorphic form A has been used almost exclusively in compositions. B. Hegedüs and S. Görög, *J. Pharmaceutical & Biomedical Analysis*, Vol. 3, No. 4, pp.303-313, 1985. Secondly, there is the problem that cimetidine has a very bitter taste and palatability of oral compositions is a major consideration.

It is clear that there has been a need for compositions of cimetidine which are liquid based and are palatable. Cimetidine is absorbed almost exclusively in the small intestine and liquid-based compositions offer the possibility that they could be absorbed more quickly and more efficiently than tablet compositions, particularly tablet compositions which have been coated to minimise unpleasant tastes. However, with solutions of cimetidine, the unpleasant bitter taste is a particular problem. Suspensions of cimetidine could in principle offer the advantage of being more palatable but until recently no stable suspension compositions of cimetidine have been described or sold. Some companies have tried to meet the apparent need for such a product by selling cimetidine powder or granules in sachets which can be extemporaneously mixed with water to produce suspension compositions.

EPA 0 138 540-A describes suspensions containing cimetidine and the preferred examples are buffered solutions of high viscosity. Because of the high viscosity, such suspensions are not easily poured from a bottle and consequently are usually formulated in sachets.

Aqueous suspensions of cimetidine polymorph A are thermodynamically unstable and it is found that when many such suspensions are prepared having relatively low viscosity, they are likely, when subjected to fluctuating temperatures, to undergo polymorphic transition into the polymorphic B form. This polymorphic transition, forms polymorph B in situ as very long needle-like crystals, which makes the suspensions lumpy and non-homogeneous thereby introducing dosage inaccuracy and giving rise to an unpleasant mouth feel.

It is an object of this invention to provide a suspension of cimetidine which is stable and, in particular, is of relatively low viscosity such that it can be easily poured from bottle and easily administered using a spoon or like

device so that various dosages can be exactly and accurately measured. It is also an object of this invention to form a stable composition to which other ingredients such as antacids or alginates can be added.

We have now found that by preparing suspensions from cimetidine polymorph B, the problem of polymorphic transition and the growth in situ of long needle-like crystals can be avoided.

According to the invention, there is provided a stable pharmaceutical composition suitable for oral administration comprising a suspension of particulate cimetidine in an aqueous phase having a pH of at least 7, and a suspending agent, wherein substantially all of the cimetidine present is of the polymorphic B form, and optionally any other pharmaceutical excipients.

Preferably at least 90% and particularly preferably at least 95% of the cimetidine is in the polymorphic B form. It is preferred that substantially no polymorph A is present.

By stable is meant a suspension which is capable of remaining in a pharmaceutically acceptable condition for a prolonged period, for example at least six months, preferably at least a year and most preferably for more than three years. Thus there should not be significant crystal growth, and any sediment formed should be capable of being re-suspended with only mild agitation, i.e. the sediment should not take the form of a "cake" or lumps which cannot readily be re-suspended. Preferably no sediment should form at all.

It is in general preferred that the pH of the suspension is within the range 7-9.5, preferably 7.4-8.4, and particularly 7.8-8.2. It will be appreciated that the suspensions can be either buffered or unbuffered.

It is preferred that the suspensions of the present invention have a viscosity of less than 1,500 mPa.s but greater than 200 mPa.s, for example within the range 1,200 mPa.s to 500mPa.s. The skilled man will be aware that the viscosity values obtained for a given system depend on the temperature, the shear rate and the shear history. The above figures refer to freshly shaken and poured suspensions at approximately 25° C. subjected to a shear rate of 0.7 sec.⁻¹.

An advantage of suspensions having a viscosity within the range 200 mPa.s to 1,500 mPa.s is that they are readily pourable. This is in contrast to suspensions prepared from cimetidine polymorph A which frequently are required to be of a high viscosity in order to remain stable, i.e. to minimise polymorphic interconversion, the viscosity being such that they are not readily pourable. By readily pourable is meant that they are capable of being easily poured from a suitable container such as a bottle. It will be readily appreciated that where the composition is a reversible gel, it may be necessary to shake the container before pouring in order to disrupt the gel structure.

When the suspension contains alginate, the thickening effect of the alginate means that the viscosity of the suspension is generally higher than the range 200-1,500 mPa.s quoted above and typically is in the range 2,500-5,000 mPa.s for example approximately 3,500 mPa.s.

Examples of suspending agents include xanthan gum, hydroxypropylmethylcellulose, methylcellulose, carageenan, sodium carboxymethyl cellulose, and sodium carboxymethyl cellulose/microcrystalline cellulose mixtures, particularly sodium carboxymethyl cellulose/microcrystalline cellulose mixtures. Preferred suspending agents are thixotropic suspending agents

such as xanthan gum, carageenan and sodium carboxymethyl cellulose/microcrystalline cellulose mixtures and particularly preferred suspending agents are Avicel RC591, Avicel RC581 and Avicel CL611. Avicel is a trademark of FMC Corporation, and KC591, RC581 and CL611 are mixtures of microcrystalline cellulose and sodium carboxymethyl cellulose. The amount of suspending agent present will vary according to the particular suspending agent used and the presence or absence of other ingredients which have an ability to act as a suspending agent or which contribute significantly to the viscosity of the composition. In general, however, the amount of suspending agent will lie in the range 0.1-1.5% w/w of the total weight of the composition. When the suspending agent is xanthan gum, it will usually be present in an amount corresponding to 0.1-0.5% w/w of the total weight whereas when Avicel is used, the amount typically will lie in the range 0.6-1.5% w/w particularly approximately 1.2% w/w. When carageenan is used, typically this will constitute 0.5-1% w/w of the composition. Compositions containing alginate, which has a significant thickening effect, will, in general, contain lower concentrations of suspending agent in order to avoid the problem of the viscosity being so great that the composition cannot be poured.

The suspension can contain ingredients which improve its taste, for example sweeteners, bitter-taste maskers such as sodium chloride and taste-masking flavours such as contrammarum, flavour enhancers such as monosodium glutamate, and flavouring agents.

Examples of sweeteners include bulk sweeteners such as sucrose, hydrogenated glucose syrup, the sugar alcohols sorbitol and xylitol, and sweetening agents such as sodium cyclamate, sodium saccharin, aspartame and ammonium glycyrrhizinate.

A bulk sweetener will usually be present in an amount corresponding to about 15-70% w/w of the total weight of the suspension, the amount depending in part upon whether other ingredients, e.g. alginate, are present which have a thickening effect on the composition. For example, when sorbitol is used as the sole bulk sweetener and no thickener (e.g. alginate) is present, typically the dry weight of sorbitol present is in the range 35-55% w/w of the total weight of the suspension, for example at a concentration of approximately 45% w/w.

When hydrogenated glucose syrup (solids content approximately 74%) is used as the sole bulk sweetener, typically it is present as 55-70% w/w of the suspension, for example at a concentration of approximately 65% w/w (equivalent to 49% solids). It will be appreciated that combinations of bulk sweeteners can be used, for example combinations of sorbitol and hydrogenated glucose syrup, or sucrose and sorbitol.

Other excipients which can be used include humectants such as propylene glycol and glycerol and colourants such as titanium dioxide.

Typically the total quantity of humectant present is in the range 0-10% w/w. Thus, for example, propylene glycol and glycerol can each be present in an amount approximating to 4% w/w.

It is preferred that the suspensions contain preservatives to prevent microbial contamination. Examples of preservatives are the alkylparabens, particularly propylparaben and butylparaben. Parabens tend to be unstable at high pH values and hence most suitably are employed when the pH is below 8.2.

Preferably the suspension contains from 1.0 to 4.5% w/w cimetidine.

In one preferred embodiment of the invention there is provided a composition containing 1.5-3.5% w/w of cimetidine, 35-45% w/w of water, 35-55% of sorbitol, 0-10% w/w of a humectant which is propylene glycol and/or glycerol, 0.6-1.5% W/w of a mixture of sodium carboxymethyl cellulose and microcrystalline cellulose and optionally other pharmaceutical excipients.

The compositions of this invention can optionally contain an antacid. An antacid is a pharmaceutically acceptable basic material of sufficient neutralising capacity to neutralise stomach acid. Examples of antacids are aluminium hydroxide, magnesium hydroxide, magnesium carbonate, calcium carbonate and co-dried gels for example aluminium hydroxide-magnesium carbonate co-dried gel. Preferably the amount of antacid is such that a unit dose contains 10-30 milliequivalents.

In a further embodiment of the invention, there is provided a suspension of cimetidine polymorph B additionally containing alginate.

The purpose of the alginate is to form a raft of mucus which floats on the contents of the stomach thereby preventing gastro-oesophageal reflux (GORD) or reducing its symptoms. Usually a carbonate salt such as potassium bicarbonate or sodium bicarbonate is added. Reaction of the carbonate with the acidic gastric juices generates carbon dioxide which aerates the alginate raft, reducing its density and thereby enabling it more easily to float on the stomach contents.

When bicarbonate salts are present, the suspensions are maintained at a pH of 7.5 or more in order to prevent premature decomposition and evolution of carbon dioxide. Typically the pH is maintained in the range 7.8-8.4, for example by using a buffering agent such as a phosphate buffer.

In order to avoid too great an increase in the viscosity of the suspension, a low viscosity grade of alginate is used. Low viscosity grades of alginate suitable for use in the compositions of the present invention will generally have a viscosity of 4-10 mPa.s in 1% aqueous solution at 20° C. Alginates are polymers composed of mannuronic and guluronic acid monomer units. The ratio of mannuronic to guluronic acids determines the raft-forming properties of the alginate and, in general, alginates having a high guluronic-mannuronic ratio (e.g. 70% guluronic acid) form the strongest rafts. Alginates containing such high levels of guluronic acid are preferably used in the compositions of the present invention, and one such alginate is Protanal LFR 5/60.

The concentration of alginate will be chosen so as to optimise the raft-forming ability of the suspension whilst not adversely affecting the pourability of the suspension by increasing the viscosity too much.

In practice, the concentration of alginate (w/w) typically is less than 10% relative to the total weight of the suspension. Preferably the alginate is present at a concentration of approximately 5%.

The alginate is usually present as an alkali metal salt such as sodium alginate.

A problem which has been encountered in the preparation of cimetidine alginate suspensions is that the cimetidine can be oxidised to its sulphoxide. Cimetidine sulphoxide is a known metabolite of cimetidine and whereas its presence in the suspension does not give rise to problems of toxicity, the sulphoxide is essentially inactive as an H₂-antagonist and thus the oxidation of

cimetidine may lead to a reduction in efficacy of the composition.

The mechanism of sulphoxide formation is not known. The addition of standard antioxidants such as propyl gallate and sodium sulphite does not inhibit the formation of the sulphoxide. Moreover certain chelating agents such as polyphosphates and trisodium citrate have been added but have also been found to be ineffective in preventing oxidation. However, it has now surprisingly been found that sulphoxide formation can be significantly inhibited by the addition of ethylenediaminetetraacetic acid (EDTA) and salts thereof.

In a preferred aspect of this invention, therefore, there is provided a pharmaceutical suspension as hereinbefore defined comprising cimetidine polymorph B and, additionally, alginate and EDTA or a salt thereof. Typically the EDTA is present in an amount from approximately 0.05% (w/w) to approximately 0.25% (w/w) of the total weight of the suspension; particularly approximately 0.1% (w/w). The EDTA is usually added as a salt. Particularly the disodium salt.

In the compositions of the present invention, typically the particle size of the cimetidine is such that in the final suspension 80% by weight of the particles are less than 200 μ in size but are greater than approximately 5 μ in size. The sizes referred to are the apparent diameters as measured by a Malvern 3600E Laser particle Sizer (supplied by Malvern Instruments Limited, Spring Lane, Worcester, U.K.).

The compositions of the present invention can be prepared by mixing the cimetidine polymorph B with the suspending agent, and any other ingredients to be included, to form a suspension.

The cimetidine polymorph B can be prepared by forming a solution of cimetidine acetate in aqueous isopropanol (10% isopropanol), clarifying by filtration and basifying with aqueous ammonia (10% excess) as described in Appendix A. The mixture is then stirred to allow the polymorph B to crystallise completely, then the product is isolated by filtration, washed well with water and dried to constant weight.

The invention is illustrated but in no way limited by the following examples. In the examples, all references to cimetidine refer to the B polymorph unless otherwise stated.

EXAMPLE 1

Cimetidine Suspension (200 mg in 10 ml)

INGREDIENTS	QTY (g)	UNIT DOSE mg/10 ml
Cimetidine Base (B Polymorph)	120.0	200
Avicel RC591	90.0	150
Water	1500.0	2500
Propylene Glycol	300.0	500
Glycerol	300.0	500
Butylparaben	6.0	10
Propylparaben	3.0	5
Sodium Saccharin	2.4	4
Vazilla (Firmenich 54.286C)	3.0	5
Cream (FDO FC 900772)	6.0	10
Titanium Dioxide 50% in Glycerol	24.0	40
Sorbitol 70% in water*	4940.0	8234

*Sorbitol 3460 g, Water 1480 g.

PROCESS

The Avicel is dispersed in demineralised water using a low shear propeller mixer and the resulting dispersion

is passed through a premier colloid mill (premier Colloid Mills Ltd., Walton-on Thames, Surrey, U.K.) on high speed at 25 μ gap. The Avicel high shear dispersion is mixed with 3.6 kg of the sorbitol 70% solution and to the mixture is added the glycerol followed by a solution of the parabens in propylene glycol. The flavourings and the titanium dioxide paste are then added with stirring to give a homogenous mixture. Cimetidine is then added followed by the remainder of the sorbitol to give a total volume of 6 liters. The batch is then passed through a colloid mill on low speed set to the smallest possible gap (approx 25 μ) such that the milling process does not cause the temperature of the milled material to exceed 35° C. The pH of the resulting suspension is approximately 7.8.

EXAMPLE 2

Cimetidine Suspension (200 mg in 5 ml)

This has a similar composition to that described in Example 1 except that the quantity of cimetidine is doubled

EXAMPLE 3

Cimetidine Suspension in Hydrogenated Glucose Syrup

This has a composition analogous to that described in Example 2 except that instead of sorbitol 70%, an equivalent volume of hydrogenated glucose syrup (74% solids) is used as the vehicle.

EXAMPLE 4

Determination of the viscosities of the formulations of Examples 1 to 3, 6 and 8

The viscosities of the compositions of Examples 1 to 3, 6 and 8 were determined using a Rheomat 30 Rheometer supplied by Contraves of Switzerland. The measurements were conducted at 27° C. and the results are shown in Table 2.

TABLE 2

Shear Rate (sec. ⁻¹)	Apparent Viscosity (η_a) (mPa · s)			
	Examples 1 and 2	Example 3	Example 6	Example 8
0.7	700	1000	3400	1000
7	400	800	1000	500
70	200	300	500	200
700	100	200	300	100

EXAMPLE 5

Comparative Stabilities of Suspensions containing Polymorph A and Suspensions containing Polymorph B

(i) Compositions as described in Example 1 were subjected to isothermal storage for one year at temperatures of 4°, 22°, 30° and 40° C. Microscopic examination after this time indicated that no crystal growth had occurred.

The composition of Example 1 was also subjected to 50 thermal cycles between 10° and 30° C. No crystal growth was detected following this test.

(ii) Compositions identical to those described in Example 1, except that cimetidine polymorph A was used instead of cimetidine polymorph B, were also subjected to stability tests. The median particle size in the freshly prepared suspensions was approximately 40 μ .

After 5 months at room temperature filaments 750µ in length were observed upon microscopic examination.

At ten months filaments up to 2.5 mm were observed along with filamentous clusters up to 1 mm in length.

Upon storage at 30° C. for 3 days, filaments up to 2.5 mm in length were observed and after storage at 40° C. for 3 days a large filamentous aggregate of 4 mm overall length was detected.

After thermal cycling, 10°-30° C., 9 cycles, numerous feather-like clusters up to 800µ long and 200µ wide were formed. One feather-like aggregate of 1.8 mm length was detected.

EXAMPLE 6

100 Mg Cimetidine/Sodium Alginate Suspension

INGREDIENTS	UNIT DOSE QUANTITY (g/100 ml)
Cimetidine Base	2.0
Sodium Alginate (Protanal LFR 5/60)	5.0
Potassium Bicarbonate	3.18
Propylene Glycol	5.0
Glycerol	5.0
Avicel CL-611 (Microcrystalline cellulose and sodium carboxymethylcellulose)	0.2
Sorbitol Solution BP (70% w/w)	22.0
Hydrogenated Glucose Syrup (Lycasin 80/55)	4.0
Butylparaben	0.1
Propylparaben	0.05
Ethyleodiaminetetraacetic acid (disodium salt)	0.1
Sodium dihydrogen orthophosphate dihydrate	0.31
Di-Sodium hydrogen orthophosphate dodecahydrate	0.475
Sodium Saccharin	0.02
Passion Fruit Flavour	0.01
Peppermint Flavour	0.02
Titanium Dioxide in 50% Glycerol	0.8
Demineralised Water	to 100 ml

PROCESS

The hydroxybenzoates were dissolved in warm propylene glycol and to the resulting solution was added the glycerol. After the solution had cooled to room temperature, the cimetidine was added with stirring to give a smooth slurry.

A sodium alginate mixture was prepared by dissolving the disodium edetate in demineralised water and then dispersing the sodium alginate in the solution using a high shear homogeniser.

The cimetidine slurry sorbitol solution, hydrogenated glucose syrup and sodium alginate mixture were added to a dispersion of the Avicel in demineralised water and the resulting mixture was stirred until homogenous. The remaining ingredients were added, additional demineralised water being added as necessary to give the correct volume. Finally, the suspension was passed through a colloid mill set at low speed as described in Example 1.

EXAMPLE 7

200 mg/5 ml Cimetidine/Magnesium hydroxide/Aluminium hydroxide Suspension

	g/100 ml	% (w/w)
Cimetidine	4	3.31
Magnesium hydroxide	4	3.31

-continued

	g/100 ml	% (w/w)
Aluminium hydroxide (as Al ₂ O ₃)	2.4	1.98
Xanthan	0.3	0.25
Propylparaben	0.05	0.041
Butylparaben	0.10	0.082
Propylene glycol	5.0	4.13
Glycerol	2.0	1.65
Sorbitol (70%)	75	62.0
Water	to 100 ml.	

EXAMPLE 8

100 mg/5 ml Cimetidine/Magnesium hydroxide/Aluminium hydroxide Suspension

	g/100 ml	% (w/w)
Cimetidine	2	1.65
Magnesium hydroxide	4	3.31
Aluminium hydroxide (as Al ₂ O ₃)	2.4	1.98
Xanthan	0.3	0.25
Propylparaben	0.05	0.041
Butylparaben	0.10	0.083
Mint Flavouring	0.10	0.083
Propylene Glycol	5.0	4.13
Glycerol	2.0	1.65
Sucrose	35	28.9
Sorbitol (70%)	25	20.7
Water	to 100 ml.	

EXAMPLE 9

100 mg/5 ml Cimetidine/Calcium Carbonate Suspension

	g/100 ml	% (w/w)
Cimetidine	2	1.51
Calcium carbonate	11.7	8.86
Avicel RC591	1.5	1.14
Propylparaben	0.05	0.038
Butylparaben	0.10	0.076
Sodium saccharin	0.04	0.030
Vanilla	0.05	0.038
Cream	0.10	0.076
Titanium dioxide (50%)	0.4	0.30
Propylene glycol	5.0	3.78
Glycerol	5.0	3.78
Water	25	18.93
Lycasin (hydrogenated glucose syrup)	to 100 ml	61.42

EXAMPLE 10

Cimetidine/Calcium carbonate/Magnesium hydroxide Suspensions

	g/100 ml	(w/w)
Cimetidine	2	1.5
Calcium Carbonate	10	7.52
Magnesium hydroxide	1	0.75
Avicel RC591	1.5	1.13
Propylparaben	0.05	0.038
Butylparaben	0.10	0.075
Sodium Saccharin	0.04	0.03
Vanilla	0.05	0.038
Cream	0.10	0.075
Titanium dioxide (50%)	0.4	0.30
Propylene glycol	5.0	3.76
Glycerol	5.0	3.76
Water	25	18.79

-continued

	g/100 ml	(w/w)
Lycasin (hydrogenated glucose syrup)	to 100 ml	62.24

APPENDIX A

Preparation of Cimetidine Polymorph B

To a stirred suspension of 252 grams of cimetidine polymorph A in 2.0 liters of water and 250 ml of isopropanol was added a solution containing 60 grams of acetic acid in 125 ml water. The mixture was stirred and the resulting solution was clarified by filtration. To the resulting clear solution was added with agitation a solution containing 68 ml of concentrated ammonia (27% w/w) in 125 ml of water. Following precipitation of the cimetidine base, the mixture was heated to 40°-45° C., and held there for 24 hours. The appropriate in-process checks* after this time indicated that the solid was completely form "B". The mixture was cooled, the product isolated by filtration, and washed well with water. The solid was dried at 60° C. to yield 240 grams (95%) of crystalline cimetidine "B" having a melting point of 142.5°-144° C. * An appropriate process check is to obtain an infra-red spectrum of the product and calculate the ratio of the peak heights of the absorbance bands at 1004 and 993 cm^{-1} . The concentration of polymorph C is then determined by reference to a calibration curve obtained by plotting the peak ratios for various standard mixtures of polymorph C and polymorph B.

The above-mentioned process for preparing cimetidine polymorph B is also disclosed and is claimed in a co-pending European patent Application which derives priority from British patent Application No. 8618846 filed on 1st August 1986. The term "polymorph B" as used hereinabove includes a reference to crystalline cimetidine prepared according to the said process.

What is claimed is:

1. A stable pharmaceutical composition suitable for oral administration comprising a suspension of an effective histamine H₂-antagonist amount of particulate cimetidine in an aqueous phase wherein substantially all of the cimetidine present is of the polymorphic B form.

2. A composition according to claim 1 wherein at least 95% of the cimetidine is in the polymorphic B form.

3. A composition according to claim 1 having a pH in the range 7-9.5.

4. A composition according to claim 1 wherein the viscosity of the suspension, as measured at 25° C. and at

a shear rate of 0.7 sec^{-1} , is in the range 200 mPa.s to 1,500 mPa.s.

5. A composition according to claim 4 wherein the viscosity is 500 mPa.s to 1,200 mPa.s.

6. A composition according to claim 1 which contains a suspending agent.

7. A composition according to claim 6 wherein the suspending agent is a mixture of sodium carboxymethyl-cellulose and microcrystalline cellulose, which mixture is present in an amount in the range of from about 0.6 to about 1.5% w/w of the total weight of the composition.

8. A composition according to claim 1 wherein at least 80% of the cimetidine particles have an apparent diameter in the range of from about 5 μ to about 200 μ .

9. A composition according to claim 1 which contains an antacid or alginate.

10. A composition according to claim 1 containing 1.5-3.5% w/w of cimetidine, 35-15% w/w of water, 35-55% w/w of sorbitol, 0-10% w/w of a humectant selected from the group consisting of propylene glycol or glycerol and 0.6-1.5% w/w of a mixture of sodium carboxymethyl cellulose and microcrystalline cellulose.

11. A composition according to claim 9 which contains EDTA or a salt thereof in an amount from about 0.05% w/w to about 0.1% w/w of the total weight of the composition.

12. A composition according to claim 1 wherein at least 90% of the cimetidine is in the polymorph B form.

13. A process for producing a stable pharmaceutical composition comprising dispersing a suspending agent with a substantially pure effective amount of histamine H₂ antagonist Polymorph B cimetidine into a suspension such that the viscosity of the resulting suspension is less than 1500 mPa's and greater than 200 mPa's.

14. A stable pharmaceutical composition, which is readily pourable, suitable for oral administration comprising a suspension of an effective histamine H₂-antagonist amount of a particulate cimetidine in an aqueous phase wherein substantially all of the cimetidine present is of the polymorphic B form.

15. A composition according to claim 14 wherein the resulting viscosity of the suspension, as measured at 25° C. and at a shear rate of 0.7 sec^{-1} , is in the range of 200 mPa's to 1,500 mPa's.

16. A stable pharmaceutical composition suitable for oral administration comprising an alginate, and a suspension of an effective histamine H₂-antagonist amount of a particulate cimetidine in an aqueous phase wherein substantially all of the cimetidine present is of the polymorphic B form.

• • • • •

United States Patent [19]

Graboyes et al.

[11] Patent Number: 4,786,735

[45] Date of Patent: Nov. 22, 1988

[54] PROCESS FOR PREPARING CIMETIDINE POLYMORPH B

[75] Inventors: Harold Graboyes, Wynnewood;
David S. Kirkpatrick, Broomall, both
of Pa.

[73] Assignee: Smithkline Beckman Corporation,
Philadelphia, Pa.

[21] Appl. No.: 77,721

[22] Filed: Jul. 27, 1987

[30] Foreign Application Priority Data
Aug. 1, 1986 [GB] United Kingdom 8618846

[51] Int. Cl.⁴ C07D 233/64

[52] U.S. Cl. 548/342

[58] Field of Search 548/342

[56] References Cited
FOREIGN PATENT DOCUMENTS

56-104868 8/1981 Japan 548/342
1543238 3/1979 United Kingdom 548/342
2108117 5/1983 United Kingdom 548/342

OTHER PUBLICATIONS

B. Hegedus et al., *Journal of Pharmaceutical & Biomedical Analysis*, vol. 3, No. 4; pp. 303-313; 1985.

Primary Examiner—Richard A. Schwartz
Attorney, Agent, or Firm—Joseph A. Marfino; Stuart R. Suter; Alan D. Lourie

[57] ABSTRACT

A novel process for preparing cimetidine polymorph "B" comprises precipitating cimetidine from an aqueous-alcoholic solution of an acid addition salt. The precipitation is conducted at a temperature of above 15° C.

12 Claims, No Drawings

PROCESS FOR PREPARING CIMETIDINE POLYMORPH B

The present invention relates to a process for preparing cimetidine polymorph B in a substantially pure crystalline form.

Cimetidine (N-methyl-N'-cyano-N''-[2-((5-methyl-4-imidazolyl)methylthio)ethyl]-guanidine) is a potent histamine-H₂-receptor antagonist which has been used for a number of years in the treatment of duodenal and benign gastric ulceration, recurrent and stomal ulceration, oesophageal reflux disease and other conditions where reduction of gastric acid by cimetidine has been shown to be beneficial, for example persistent dyspeptic symptoms with or without ulceration.

It is well known (B. Hegedüs and S. Görög, *J. Pharm. & Biomed. Anal.* 1985, 3, 303-13) that cimetidine exhibits polymorphism, that is to say it can exist in any of a number of different crystalline forms. To date, four crystalline forms (hereinafter referred to as polymorphs) of the anhydrous base, and three polymorphs of the monohydrate of the base have been characterized. The anhydrous forms have been designated as polymorphs A-D whilst the hydrated forms have been designated polymorphs M1-M3.

It is generally recognized that substantially all formulations of cimetidine currently marketed contain polymorph A. Polymorph A can be prepared by recrystallizing cimetidine from a non aqueous organic solvent, particularly isopropanol, as described in GB No. 1,543,238. This process has been shown to be highly reproducible and to result in cimetidine which is easy to filter and has good bulk handling and formulation properties.

A method of preparing another polymorph, polymorph D (sometimes referred to as polymorph Z), has also been disclosed in GB No. 2,108,117A.

In contrast to polymorphs A and D, polymorphs B and C are disclosed by Hegedüs as being difficult to handle, due at least in part to their thixotropic properties in aqueous suspension which make separation by conventional methods such as filtration and centrifugation very difficult. This has also been the experience of the applicants up until the time of making the present invention.

Hegedüs et al further disclose that cimetidine polymorph B can be prepared by slowly cooling a hot (70°-80° C.) aqueous solution of 15% w/w cimetidine but indicate that this process is less reproducible than the known processes for preparing polymorphs A and D. A possible reason for the relatively poor reproducibility is the apparent criticality of the rate of cooling and the concentration. Thus, it is disclosed that polymorph C is obtained by rapid cooling of a hot (50°-60° C.) 5% w/w aqueous solution of cimetidine whereas polymorph M1 is obtained by pouring a hot 15% aqueous solution of cimetidine into a five fold excess of ice. The picture is further confused by the disclosure of Prodic Kojic et al, (*Gazz. Chim. Italiana*, 1979, 109, 539) which suggests that allowing a hot solution of cimetidine, solvent: solute ratio of 10 ml./g., to cool to room temperature gives rise to polymorph C whereas allowing solutions having solvent: solute ratios of 30 and 60 ml/g to cool under the same conditions gives rise in each instance to a mixture of polymorph M1 and polymorph B. It therefore seems likely that the problems encountered in the prior art methods for preparing

polymorph B are due at least in part to contamination of the polymorph B with other polymorphs, most notably polymorph C.

In order to render possible the development of formulations comprising cimetidine polymorph B, it is necessary that there should exist a method for preparing the B polymorph which is reproducible, which gives rise to cimetidine of the required degree of polymorphic purity and is relatively easy to handle and formulate.

The process of this invention not only provides the above advantages but provides a rapid and efficient method for preparing cimetidine B using standard process equipment. The product can be easily separated by conventional techniques such as filtration and centrifugation. This is due to the fact that the polymorph B is obtained in a fluid slurry instead of a thixotropic mixture.

It has now been found that cimetidine polymorph B can be obtained in a high state of polymorphic purity, and in a form which has good bulk handling and formulation properties, by precipitating cimetidine from a solution of an acid addition salt thereof in water containing 7-20% (v/v) of a C₁₋₄ alcohol by addition of a base, the precipitation being conducted at a temperature above 15° C. The precipitation typically is conducted at a temperature of less than 55° C. and usually approximating to, or in excess of, ambient temperature, e.g. 20°-30° C., preferably in the range 25°-30° C. Optionally, seed crystals consisting of approximately 100% polymorph B can be added after addition of the base in order to assist the crystallization process.

On occasions, very small quantities of cimetidine C are initially formed, usually no more than 5% by weight of the total yield. These can be converted into polymorph B by ageing the suspension. Usually the suspension is aged by being held at a temperature in the range from approximately ambient temperature to about 60° C., for example in the range 40°-45° C. The suspension is maintained under such conditions until the appropriate process checks indicate that substantially all of the cimetidine is in the polymorph B form. An appropriate process check is to obtain an infra-red spectrum of the product and calculate the ratio of the peak heights of the absorbance bands at 1004 and 993 cm⁻¹. The concentration of polymorph C is then determined by reference to a calibration curve obtained by plotting the peak ratios for various standard mixtures of polymorph C and polymorph B. The spectral characteristics of polymorph B prepared according to the process of the present invention are set forth in Table 1.

Cimetidine polymorph B prepared according to the present process has a polymorphic purity of at least 90%, usually at least 95% and most usually in excess of 98%.

Examples of C₁₋₄ alcohols are methanol and isopropanol; a preferred alcohol being isopropanol. The concentration of alcohol is preferably in the range 8-15% (v/v) and most preferably is in the range 10% to 12.5%.

The cimetidine acid addition salt can be, for example, the acetate, hydrochloride, sulfate, maleate or fumarate. In order to minimize or prevent hydrolysis of the cimetidine it is preferable that the acid addition salt is formed from a carboxylic acid, and particularly preferably the acid addition salt is the acetate. The acid addition salt can be formed in situ by dissolving cimetidine base in an aqueous solution of the appropriate acid, or it can be pre-formed and simply dissolved in the aqueous phase.

The base, addition of which causes cimetidine base to precipitate, can be an inorganic base or an organic base. Examples of such bases are ammonium hydroxide, sodium hydroxide, potassium hydroxide, sodium carbonate, monomethylamine and triethylamine. Preferably the base is ammonium hydroxide. In general, sufficient base is added to adjust the pH to a value approximately nine.

It is preferred to add the base at such a rate that precipitation of cimetidine does not occur to any significant extent until the addition of the base has been completed.

The following examples illustrate the process of the present invention but are not intended in any way to be construed as a limitation thereof.

EXAMPLE 1

To a stirred suspension of 252 grams of cimetidine form "A" in 2.0 liters of water and 250 ml of isopropanol was added a solution containing 60 grams of acetic acid in 125 ml water. The mixture was stirred and the resulting solution was clarified by filtration. To the resulting clear solution was added at room temperature, with agitation, a solution containing 68 ml of concentrated ammonia (27% w/w) in 125 ml of water. The precipitated mixture was stirred, heated to 40°-45° C., and held there for about 24 hours. The appropriate in process checks after this time indicated that the solid was completely form "B". The mixture was cooled, the product isolated by filtration, and washed with water. The solid was dried at 60° C. and yielded 240 grams (95%) of crystalline cimetidine "B" having a melting point of 142.5°-144° C.

EXAMPLE 2

Bulk Manufacture of Cimetidine Polymorph B	
Raw materials:	
cimetidine	140.0 kg
acetic acid	33.3 kg
ammonia (SG 0.88)	10.39 kg
isopropanol	140.00 liters
cimetidine polymorph B seed crystals	100.00 g.

The cimetidine was added to an agitated solution of the isopropanol (140 L) in water (980 L) to form a slurry. A solution of acetic acid (33.3 kg) in water (70 L) was prepared and added to the slurry of cimetidine over a period of approximately 15-20 minutes, care being taken to ensure that the temperature remained in the range 25°-30° C. Following addition of the acid, the mixture was stirred for one hour to achieve complete solution. The pH of the resulting solution was approximately 5.9. The solution was then passed through a filter into another vessel.

Concentrated ammonia (SG 0.88) (10.39 kg) was added to filtered water (70 L) to give a solution of ammonium hydroxide. The resulting ammonium hydroxide solution was then added via a dip pipe into the vortex of the stirred solution of cimetidine over ca. 15-30 minutes keeping the temperature between 25° and 30° C. After addition was complete, the seed crystals were added, and the cimetidine was allowed to crystallize completely, where necessary adding water (up to 280 L in 140 L charges) if the slurry became too thick. Infra red spectral analysis of the product was then conducted in order to check the polymorphic purity, and particularly the levels of polymorph C. If there was substantially no polymorph C present, the crystalline

slurry was cooled, stirred for one hour and then isolated by centrifugation. If detectable quantities of polymorph C were present, the slurry was warmed to 40°-45° C. and held at this temperature for ca. 12-20 hours or until such time as the quantity of polymorph C present was within acceptable limits. The slurry was then cooled, and the product isolated, as described above.

EXAMPLE 3

Following the procedure of Example 1 and substituting hydrochloric, sulfuric, fumaric or maleic acids for acetic acid as starting materials to form their respective cimetidine acid salts in solution and substituting mono methylamine for ammonia yields cimetidine polymorphic B.

TABLE I

Infra-red Spectral Absorbencies of Cimetidine Polymorph B prepared according to the process of Example 1 (Spectrum obtained from a KBr Pellet) (cf Hegedus and Goros, J. Pharm. & Biomed. Anal., 1985, 3, 303-13)

Absorbance Bands (cm ⁻¹)	
3236	1192
3166	1184 Triplet; s.i.; m.i.
3076	1176
3040	1115
2997	1096
2947	1066
2933	1030
2848	1020
2174 s.b.; s.i.	1004
1604 doublet; moderately	993
1587 sharp; s.i.	966
1488	952
1464	855
1449	839
1429	816
1417	790
1374	769
1349	743
1306	716
1286	671
1270	653
1253	644
1236 Triplet; s.b.;	628
1230 m.i.	423
1219	

s.b. = sharp bands
s.i. = strong intensity
m.i. = medium intensity

We claim:

1. A process for preparing cimetidine, substantially all of which is in the polymorph B form, which process comprises precipitating cimetidine from a solution of an acid addition salt thereof in water containing 7-20% (v/v) of a C₁₋₄ alcohol by addition of a base, the precipitation being conducted at a temperature above 15° C.
2. A process according to claim 1 wherein the C₁₋₄ alcohol is methanol.
3. A process according to claim 2 wherein the C₁₋₄ alcohol is isopropanol.
4. A process according to claim 1 wherein the alcohol is present at a concentration (v/v) of 8-15%.
5. A process according to claim 4 wherein the alcohol is present at a concentration (v/v) in the range 10-12.5%.
6. A process according to claim 1 wherein the acid addition salt is a carboxylate.
7. A process according to claim 1 wherein the acid addition salt is selected from the group consisting of acetate, hydrochloride, sulfate, maleate or fumarate.

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8. A process according to claim 7 wherein the acid addition salt is the acetate.

9. A process according to claim 1 wherein the base is selected from the group consisting of ammonium hydroxide, sodium hydroxide, potassium hydroxide, sodium carbonate, monomethylamine or triethylamine.

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10. A process according to claim 9 wherein the base is ammonium hydroxide.

11. A process according to claim 1 wherein the precipitation is conducted at a temperature in the range 25°-30° C.

12. A process according to claim 1 wherein a seed crystal of cimetidine polymorph B is employed.

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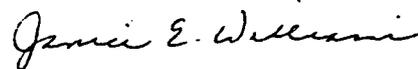
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PATENT CERTIFICATION [21 CFR 314.50 (D)]

Tagamet HB 200®, Cimetidine Suspension 200 mg/20mL
New Drug Application For Human Use

In the opinion and to the best knowledge of SmithKline Beecham Corp, the undersigned declares that the two patents listed in Section 13 under PATENT INFORMATION are the only patents that are applicable for this new drug application.



Janice E. Williams, Esq.
Vice President, Consumer Healthcare
Corporate Intellectual Property - U.S.
SmithKline Beecham Corporation

CSO/Kacuba

NDA 20-951

SmithKline Beecham Consumer Healthcare
Attention: Robert Harris
Senior Specialist, Regulatory Affairs
1500 Littleton Road
Parsippany, NY 07054-3884

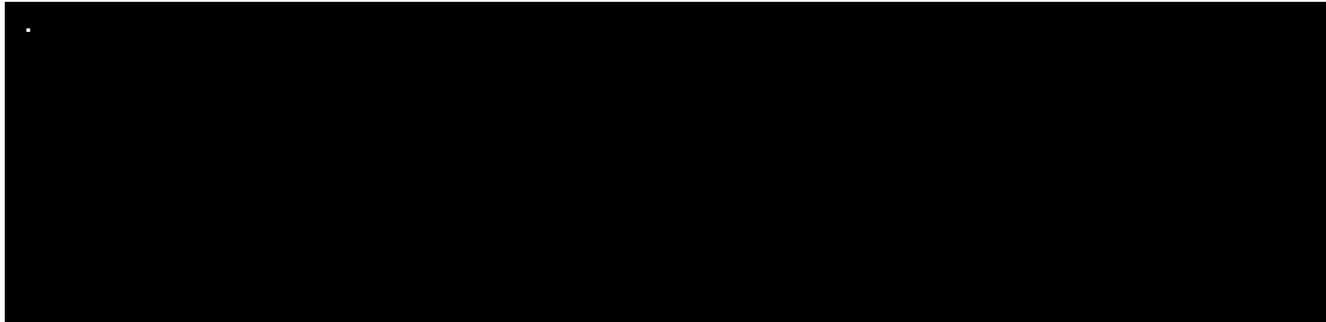
APR 2 1999

Dear Mr. Harris:

Please refer to your pending December 29, 1997 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nonprescription Tagamet HB 200 (cimetidine) Suspension.

We also refer to your submissions dated November 20, 1998 and January 8, 1999.

We have completed our review of the chemistry section of your submission and have the following comments and information requests:



We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Alice Kacuba, Regulatory Health Project Manager, at
(301) 827-7450.

Sincerely,

/s/

[Redacted Signature]

4/2/99

Eric P. Duffy, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal
and Coagulation Drug Products, (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

CS/Kacuba

NDA 20-951

SmithKline Beecham Consumer Healthcare
Attention: Robert Harris
1500 Littleton Road
Parsippany, NJ 07054-3884

JAN 21 1999

Dear Mr. Harris:

We acknowledge receipt on January 11, 1999 of your January 8, 1999 resubmission to your new drug application (NDA) for Non-Prescription Tagamet HB 200® (cimetidine) Suspension.

This resubmission contains additional labeling information submitted in response to our December 17, 1998 action letter. This submission also references your submission dated November 20, 1998, which was not reviewed during the first review cycle.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is July 11, 1999.

If you have any questions, contact me at (301) 827-7310.

Sincerely,

/s/

1-20-99

Alice Kacuba
Consumer Safety Officer
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Archival NDA 20-951
HFD-180/Div. Files
HFD-180/A.Kacuba
DISTRICT OFFICE

APPEARS THIS WAY ON ORIGINAL

Drafted by: A.Kacuba/January 14, 1999
Initialed by: K.Johnson/January 20, 1999
final: AK/January 20, 1999
filename: c:\wpfiles\20951-CR-1-14-99

ACKNOWLEDGEMENT (AC)

CS/Kacuba

NDA 20-951

SmithKline Beecham Consumer Healthcare
Attention: Sue E. James
1500 Littleton Road
Parsippany, NJ 07054

NOV - 6 1998

Dear Ms. James:

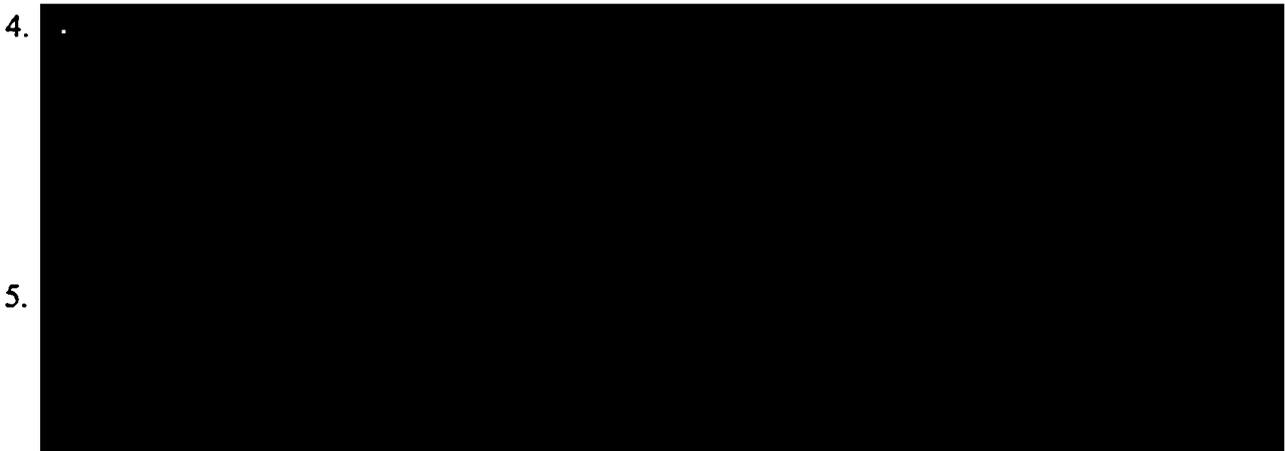
Please refer to your pending December 30, 1997 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Non-prescription Tagamet® 200 HB (cimetidine) Oral Suspension.

We also refer to your submissions dated June 16 1998.

We have completed our review of the chemistry, manufacturing and controls section of your submission and have the following comments and information requests:

1. State whether the drug substance [redacted] is processed before being used to manufacture the drug product, and if so, indicate the tests conducted.
2. State the [redacted] used to check for [redacted] during the [redacted] and clarify what is done if [redacted] are found.
3. With regards to the drug product testing, please provide the sampling plan and the rationale for it's design. Specify the number of individual product samples that will be analyzed for each test.

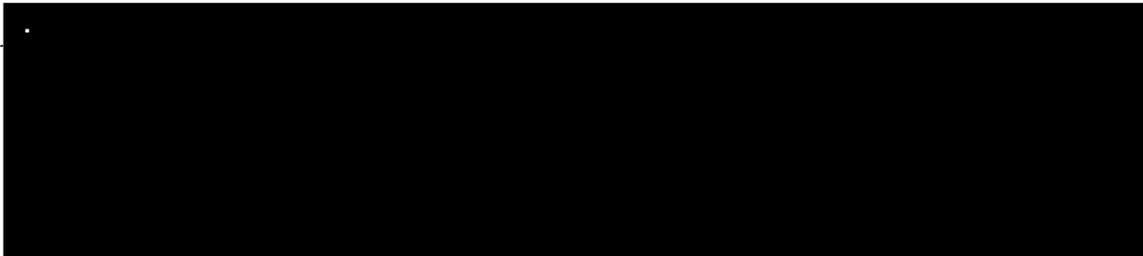
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5.

- b. Clarify if there is any overlap of this unidentified peak and the active substance peak.

c.

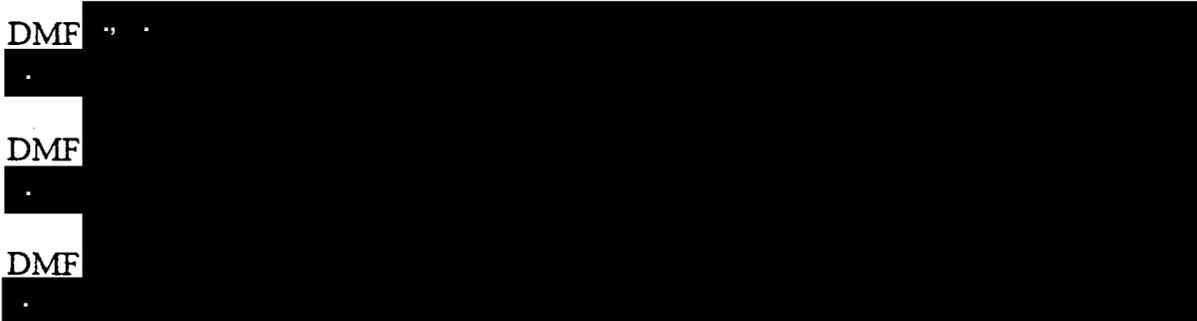


d. Clarify if the lots used in the clinical trials



We also wish to inform you that the following Drug Master Files (DMFs) are deficient:

→ DMF



→ DMF

→ DMF

The DMF holders have been notified of these deficiencies in letters dated July 14, September 24, and September 21, 1998 respectively.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Alice Kacuba, Consumer Safety Officer, at (301) 443-0487.

Sincerely,

/s/


Eric P. Duffy, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal
and Coagulation Drug Products, (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

11/6/98


APPEARS THIS WAY ON ORIGINAL

SB
SmithKline Beecham
Consumer Healthcare

August 28, 1998

09/09/98
[Redacted]

NDA 20-951

NEW CORRESP

Lilia Talarico, M.D.
Director, Division of Gastrointestinal and Coagulation Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-180)
Attention: Document Control Room 6B-30
5600 Fishers Lane
Rockville, MD 20857



Re: Response to the Agency's letter of July 31, 1998

Dear Dr. Talarico:

Please refer to our pending New Drug Application 20-951 for non-prescription Tagamet HB 200[®] (cimetidine) suspension, 200mg/20mL, and to Ms. Katie Johnson's letter of July 31, 1998, requesting the submission of all available clinical safety/efficacy and biopharmaceutical (PK and PD) data concerning use of cimetidine suspension in infants and children under 13 years of age.

A complete review of unpublished and published studies for cimetidine has revealed that no clinical data (safety/efficacy or biopharmaceutical) is available concerning the use of Tagamet HB 200[®] (cimetidine) suspension in infants and children under 13 years of age. The limited body of data available to date investigated the use of cimetidine in pediatric patients with more pronounced, underlying diseases than the approved uses (relief and prevention of heartburn) for non-prescription Tagamet HB 200[®] (cimetidine).

Due to the recent expiration (June 19, 1998) of the Waxman-Hatch exclusivity period for non-prescription Tagamet HB 200[®], leading to the introduction of generic cimetidine into the marketplace, it is the intention of SmithKline Beecham Consumer Healthcare not to investigate the use of Tagamet HB 200[®] (cimetidine) suspension in pediatric patients for the treatment of heartburn.

We trust this response is satisfactory and will enable the NDA review of OTC Tagamet HB 200[®] (cimetidine) suspension to continue without interruption. If you have any questions or comments concerning this matter, please do not hesitate to contact me at (973) 889-2513.

Sincerely,

A handwritten signature in black ink, appearing to read "Robert M. Harris".

Robert M. Harris
Senior Specialist, Regulatory Affairs

ORIGINAL

Enclosure: FORM FDA 356h

L:\BobH\Tagamet\Tagamet Susp\Response to FDA letter of July 31.doc

Kacuba

NDA 20-951

SmithKline Beecham Consumer Healthcare
Attention: Sue James
Associate Director, Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054

JUL 31 1998

Dear Ms. James:

Please refer to your pending December 29, 1997 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tagamet HB 200 (cimetidine) Suspension, 200 mg/20 ml.

A review of the National Disease and Therapeutic Index™ database of IMS Health for the use of prescription Tagamet (cimetidine) Liquid for the three year period 1995 through 1997 (sampling [redacted] US physicians) showed that [redacted] of drug appearances for Tagamet Oral Liquid were for children under the age of 13 years old (i.e. ages 0-12, inclusive). Of these [redacted] were patients aged 0-1 year old (infants). Given this information, and the fact that Tagamet (cimetidine) Liquid is not approved for use in children, it may be a reasonable expectation that the proposed drug product, Tagamet HB 200 Suspension, even if labeled for use by adults, will be used in children under 13 years of age, most of whom may be infants. Please submit all available clinical safety/efficacy and biopharmaceutical (pharmacokinetic and pharmacodynamic) data concerning use of cimetidine suspension in infants and children under the age of 13 years old.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee authorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking action on your application during this review cycle.

If you have any questions, contact Alice Kacuba, Consumer Safety Officer, at (301) 443-0487.

Sincerely,

/s/ [redacted] 7/31/98 for

Kati Johnson
Supervisory Consumer Safety Officer
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research



NDA 20-951

Food and Drug Administration
Rockville MD 20857

SmithKline Beecham Consumer Healthcare
Attention: Sue E. James
1500 Littleton Road
Parsippany, NJ 07054-3884

JAN 15 1998

Dear Ms. James:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Nonprescription Tagamet HB® 200 (cimetidine) Suspension, 200 mg/20 mL
Therapeutic Classification: Standard
Date of Application: December 29, 1997
Date of Receipt: December 30, 1997
Our Reference Number: 20-951

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 28, 1998 in accordance with 21 CFR 314.101(a).

If you have any questions, please contact me at (301) 443-0487.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/s/

 1/15/98
Michael Folkendt
Project Manager
Division of Gastrointestinal and Coagulation Drug
Products, HFD-180
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc: Archival NDA 20-951
HFD-180/Div. Files
HFD-180/CSO/M.Folkendt
DISTRICT OFFICE

Drafted by: mf/January 15, 1998
Final: 1/15/97
filename: 20951801.ACK

ACKNOWLEDGEMENT (AC)

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	<u>20951</u>	Trade Name:	<u>TAGAMET HB 200(CIMETIDINE)200MG/20ML SUS</u>
Supplement Number:		Generic Name:	<u>CIMETIDINE</u>
Supplement Type:		Dosage Form:	<u>Suspension; Oral</u>

Regulatory Action:	<u>AP</u>	Proposed Indication:	<u>1. For relief of heartburn associated with acid indigestion and sour stomach. 2. For prevention of meal induced heartburn associated with acid indigestion and sour stomach when taken right before or any time up to 30 minutes before eating food or drinking beverages that cause heartburn. 3. Can be used up to twice daily (24 hours).</u>
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ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No data was submitted for this indication, however, plans or ongoing studies exist for pediatric patients

What are the INTENDED Pediatric Age Groups for this submission?

NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy Formulation Status	<u>Adequate for SOME pediatric age groups</u>
Studies Needed Study Status	<u>STUDIES needed. Applicant has COMMITTED to doing them</u>

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:

.7-2-99: The 10-21-98 comment should have read, According to the firm, in a letter dated August 28, 1999, there is no information available in children under 12 years of age and due to the expiration of the Waxman-Hatch Exclusivity period for non-prescription Tagamet, the firm states that they do not intend to prusue exclusivity, nor do they intend to market Tagamet HB 200 for use in children under the age of 12 years of age. Jan. 1999 resubmission agreed to a Phase 4 committment to conduct a PD/safety study in children under 12 years of age.

Indicated for use down to 12 years of age. 10-21-98: The firm was requested to provide pediatric information concerning the use in children under 13 years of age. According to the firm, in a letter dated August 28, 1998, there is no information available and, due to the Waxman-Hatch Exclusivity period for non-prescription Tagamet HB 200, they do intend to market for pediatric use. Inthe January 8, 1999 submission, the firm has committed to phase 4 committment to conduct PD/safety studies in children under 12 years of age.

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Signature

Date

7-7-99

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 20951 Trade Name: TAGAMET HB 200(CIMETIDINE)200MG/20ML SUS
 Supplement Number: Generic Name: CIMETIDINE
 Supplement Type: Dosage Form: SUS

Regulatory Action: AE Proposed Indication: 1. For relief of heartburn associated with acid indigestion and sour stomach. 2. For prevention of meal induced heartburn associated with acid indigestion and sour stomach when taken right before or any time up to 30 minutes before eating food or drinking beverages that cause heartburn. 3. Can be used up to twice daily (24 hours).

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? NO

What are the INTENDED Pediatric Age Groups for this submission?
 NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Status -
 Formulation Status -
 Studies Needed -
 Study Status -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO Yes AN

COMMENTS:

Indicated for use down to 12 years of age.

Indicated for use down to 12 years of age. 10-21-98: The firm was requested to provide pediatric information concerning the use in children under 13 years of age. According to the firm, in a letter dated August 28, 1998, there is no information available and, due to the Waxman-Hatch Exclusivity period for non-prescription Tagamet HB 200, they do not plan any pediatric studies.

"expiration of" - added in 11/1998 revision to this label
Kate Sal...

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Signature



Date

10-26-98